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Effect of oral activated charcoal on quinine elimination

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The effect of repeated dose oral activated charcoal on quinine elimination has been studied following a therapeutic (600 mg) dose of quinine bisulphate to seven normal volunteers. Activated charcoal lowered quinine half-life from 8.23 ± 0.57 s.d. h to 4.55 ± 0.15 s.d. h ($P < 0.001$) and increased its oral clearance by 56%. Activated charcoal may have a role in the management of quinine poisoning.

Keywords quinine activated charcoal poisoning

Introduction

Quinine poisoning is a relatively uncommon but potentially serious condition (Bateman *et al.*, 1985; Boland *et al.*, 1985). The most serious complications of toxicity are retinal, with visual loss, and cardiological, with resultant arrhythmias and death. Although over the years a number of techniques have been advocated to enhance elimination of quinine following overdose, including forced acid diuresis, peritoneal dialysis, haemodialysis, exchange transfusion and charcoal haemoperfusion, there is now considerable evidence to suggest that none of these techniques exert a clinically useful effect (Bateman *et al.*, 1985).

It is known that quinine is efficiently absorbed *in vitro* by activated charcoal (Hayden & Comstock, 1975), and theoretically, oral activated charcoal might reduce quinine absorption from the gastrointestinal tract. Of more interest, however is the observation that for some drugs oral activated charcoal can produce significant increase in the rate of elimination from plasma, even when given at a time after absorption. It is postulated under these circumstances that enterohepatic recirculation of drug may be interrupted or alternatively, the charcoal in the gut could bind drug that diffuses back from the bloodstream into the gut lumen (Levy, 1982). In this study we have evaluated the effects of oral activated charcoal on the pharmacokinetics of oral quinine given to normal subjects at a therapeutic dose.

Methods

The protocol was approved by the local Ethics Committee and seven healthy male volunteers (mean age 21 years) agreed to participate in the experiment. For obvious reasons the study was open, but the order of treatments was randomized. On each of 2 days, separated by more than 1 week, the volunteers attended the clinical laboratory after an overnight fast. At 09.00 h a 600 mg dose of quinine bisulphate was given as tablets with 100 ml water. Blood samples were obtained before dosing with quinine, and subsequently at 3 h intervals for 15 h and at 24, 30 and 36 h. On one of the investigation days no additional treatment was given and subjects were allowed free access to food from 2 h after the dose of quinine. On the second day, 50 g activated charcoal was administered orally in an aqueous slurry of 500 ml 4 h after the dose of quinine, i.e. after lunch, with three further doses over the next 12 h which were not specifically timed to food intake. Two preparations of activated charcoal were used, Carbomix and Medicoal, and these were given alternatively, two of each to each volunteer, to reduce the risk of constipation with Carbomix or diarrhoea with Medicoal (Editorial, 1987).

Plasma samples were separated by centrifugation and quinine was measured by a fluorimetric technique (Cramer & Isaksson, 1963) following organic extraction. Samples from each subject were analysed in the same batch, within assay coefficient or variation being less than 5% at 1

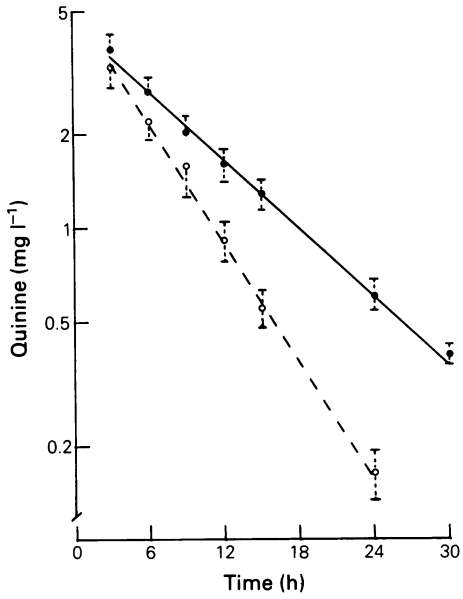

Figure 1 Plasma quinine concentrations (mg l^{-1}) following 600 mg oral quinine bisulphate in seven volunteers. (●) control, (○) with charcoal.

Table 1 Pharmacokinetic parameters in subjects (n = 7) following 600 mg quinine bisulphate

Subject	C(0) *(mg l^{-1})*	C(3) *(mg l^{-1})*	$t_{½}$*(h)*	*AUC (mg l^{-1} h)*
No charcoal				
1	3.19	2.85	8.25	38.4
2	2.78	2.71	8.67	35.2
3	6.14	4.46	6.40	56.9
4	3.83	3.99	11.09	62.1
5	4.47	3.34	8.13	52.6
6	5.04	2.11	8.17	59.9
7	7.79	5.90	6.93	72.0
Mean	4.78	3.77	8.23	53.9
s.e. mean	0.68	0.43	0.57	4.9
With charcoal				
1	3.42	2.21	4.49	22.2
2	3.12	1.87	4.38	19.7
3	6.17	3.34	3.99	35.7
4	6.69	3.35	4.53	43.7
5	6.46	3.76	4.31	40.9
6	5.20	3.00	5.07	37.6
7	7.96	5.40	5.10	58.5
Mean	5.57	3.28	4.55	36.9
s.e. mean	0.67	0.44	0.15	4.9

mg l^{-1}. The lower limit of detection was 0.05 mg l^{-1}.

The effect of activated charcoal on quinine kinetics was assessed from the plasma quinine concentration-time plot. The decline in quinine concentration was monoexponential and half-life, area under the curve extrapolated to infinity and $C(0)$ (back extrapolation to zero time) concentrations were calculated by standard methods. The oral clearance was calculated from the dose divided by AUC.

Results

There was no significant effect of activated charcoal on the calculated $C(0)$ concentration, or on the measured 3 h quinine concentration (Table 1). This suggests that the overall absorption of quinine was similar on the 2 treatment days. In no subject did the concentration of quinine in plasma 6 h after the dose exceed that at 3 h, and in all cases there was a monoexponential decline from the 3 h sample.

The half-life of quinine in subjects treated with activated charcoal was significantly shorter at 4.55 ± 0.15 h than in the same subjects when activated charcoal was not administered, 8.23 ± 0.57 h, $P < 0.001$. In consequence the area under the plasma concentration-time curve was also significantly less following treatment with activated charcoal (Table 1) and the oral clearance was increased by 56% from 11.8 ± 1.23 l h^{-1} to 18.4 ± 2.80 l h^{-1}.

There were no significant adverse effects from quinine in these subjects. However, some of the volunteers did develop constipation after activated charcoal.

Discussion

This study demonstrates that the rate of elimination of a therapeutic dose of quinine is increased when activated charcoal is administered at regular intervals commencing 4 h after the oral administration of the drug. The dose of quinine used in this experiment was clearly not toxic and the half-life of quinine was significantly shorter than that observed in patients after poisoning (Bateman *et al.*, 1985). In poisoned patients, however, it was not possible to demonstrate a significant relationship between the dose of quinine taken and the elimination half-life, so this difference may not be simply due to dose-dependent kinetics.

This study was designed to mimic the clinical circumstances of an overdose when patients often present at a time after the absorption phase. Since charcoal administration did not affect either

the 3 h concentration or the $C(0)$ concentration, we would suggest quinine absorption was similarly unaffected. We conclude from these data, therefore, that charcoal increases quinine elimination, as opposed to reducing absorption, presumably by binding quinine within the gut. There are no experimental data to suggest that quinine undergoes enterohepatic recirculation and we hypothesise that by binding quinine within the gut lumen charcoal provokes diffusion of the drug down a concentration gradient from plasma. We have used oral charcoal in two patients following quinine overdose and have found drug half-lives of about 10 h. These values contrast with half-lives of about 24 h normally observed in this group of poisoned patients (Bateman *et al.*, 1985). However, these data do not indicate whether charcoal given in this way will reduce quinine toxicity, since it is not known whether toxicity is related more closely to peak plasma drug concentrations or to the area under the curve. If the former is the case, activated charcoal will have no significant impact on quinine toxicity in overdose.

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